



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number: 0 426 468 A2

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 90311963.4

(51) Int. Cl. 5: C07C 255/41

(22) Date of filing: 01.11.90

(30) Priority: 03.11.89 GB 8924838

(43) Date of publication of application:
08.05.91 Bulletin 91/19

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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(54) Stable polymorphic form of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide and the process for its preparation.

(57) Stable and crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitro-phenyl)acrylamide may be prepared by crystallizing crude synthesis product from lower aliphatic carboxylic acid such as formic or acetic acid with a catalytic amount of hydrochloric or hydrobromic acid added. The product is a potent inhibitor of catechol-O-methyl-transferase enzyme (COMT).

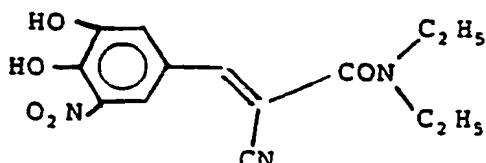
EP 0 426 468 A2

**STABILE POLYMORPHIC FORM OF
(E)-N,N-DIETHYL-2-CYANO-3-(3,4-DIHYDROXY-5-NITROPHENYL)ACRYLAMIDE AND THE PROCESS FOR
ITS PREPARATION**

The present invention relates to the stable and crystallographically essentially pure polymorphic form of N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide E-isomer, denoted (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide A, and to a process for the preparation thereof.

5 N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide described in British Patent Application No. 8727854 by the applicant is a potent inhibitor of catechol-O-methyl-transferase enzyme (COMT) and may be used pharmaceutically in the treatment of e.g. Parkinson disease. This compound with melting point 153-156 °C has proved to be a mixture of two geometric isomers, E- and Z-isomers (70-80% E-isomer and 30-20% Z-isomer) having formulae:

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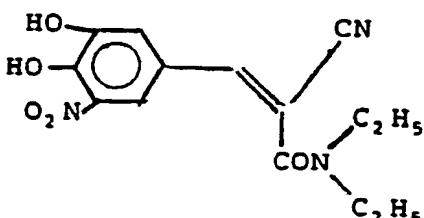


I

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E-isomer, m.p. 162 - 163 °C

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II

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Z-isomer, m.p. 148 - 151 °C

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35 (E)-N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide (I) may exist at least in two polymorphic forms A and B as shown by X-ray crystallography. The Z-isomer as well as the polymorphic form B of the E-isomer have been shown to be unstable. The Z-isomer is transformed readily into the E-isomer on the influence of heat or acids. Similarly the polymorphic form B of the E-isomer isomerises slowly to the polymorphic form A on standing at room temperature. On recrystallization of the crude synthesis product from conventional solvents such as lower aliphatic alcohols, esters or hydrocarbons, e.g. ethanol, 2-propanol, ethyl acetate or toluene, a very complicated mixture of different geometric isomers and/or polymorphic forms are generally obtained which interfere with the characterization and standardization of the drug substance. The polymorphism and geometrical isomerism may also influence on the bioavailability of the drug.

40 Surprisingly it has now been observed that crystallographically essentially pure and stable polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide is obtained in good yield, when the crude product of synthesis is recrystallized from a lower aliphatic carboxylic acid such as formic or acetic acid with a catalytic amount of hydrochloric or hydrobromic acid added. This method allows large scale production of homogenous and crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide independent of batch size or cooling rate.

"Crystallographically essentially pure" means here the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide containing a maximum of 3% and preferably a maximum of 2%

of other polymorphic forms or Z-isomer.

"Lower aliphatic carboxylic acid" means here aliphatic carboxylic acid having 1-2 carbon atoms. Examples are formic and acetic acid.

The amount of hydrochloric or hydrobromic acid appropriate for use in crystallising the crude form of the product will vary depending on the exact proportion of isomers in the crude form. Typically hydrobromic acid will be used in a weight ratio of hydrobromic acid: carboxylic acid of 1:80 to 1:120, preferably about 1:100. Typically hydrochloric acid will be used in a weight ratio of hydrochloric acid: carboxylic acid of 1:180 to 1:220, preferably about 1:200.

The crystallization from the crude product takes place preferably by first admixing the crude product and the carboxylic acid and the hydrohalic acid in any order. Most conveniently the hydrohalic acid is first admixed with the carboxylic acid and the crude product then added, although other processes, e.g. the simultaneous admixing of the three components, is also envisaged.

The crude product is preferably used in a weight ratio of crude product to carboxylic acid of 1:1.5 to 1:4 more preferably 1:2 to 1:3.

The mixture is generally heated, preferably with stirring, to a temperature at which the crude product dissolves but below the boiling point of the mixture. Typically this is 80 to 98 °C e.g. about 90 °C. The solution is then slowly cooled to about 15-20 °C and the crystalline product, essentially pure polymorphic form A, may be filtered and washed.

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Table 1.

| Typical IR-absorption bands of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide | | |
|---|---|--|
| 25 | Wavenumbers (cm^{-1}) and the relative intensities of absorption bands | |
| 30 | 3339 s | |
| 3092 w | O-H stretching | |
| 3066 w | C-H stretching, aromatic and unsaturated | |
| 3039 w | | |
| 35 | 2981 w | |
| 2938 w | C-H stretching, saturated | |
| 40 | 2217 m | |
| 1628 s | CN stretching tertiary amide C=O stretching | |
| 1607 s | C=C stretching, conjugated with C=O and aromatic ring; | |
| 45 | 1580 sh | and C=C stretching, aromatic |
| 1544 s | NO ₂ assymetric stretching | |
| 1512 m | C=C stretching, aromatic | |
| 1441 s | CH ₂ bending; assymetric CH ₃ bending; C=C stretching, aromatic | |
| 45 | 1377 s | NO ₂ symmetric stretching; OH bending |
| 50 | 1298 s | |
| 1281 sh | C-O stretching | |
| 55 | 1210 m | |
| 1165 m | C-H bending, | |
| 1150 m | aromatic | |
| 800 sh | C-H out of plane bending, aromatic | |
| 779 m | | |
| 740 m | | |
| 55 | s = strong; m = medium; w = weak; sh = shoulder | |

Experimental

Instrument: Perkin-Elmer FTIR 1725X

Detector: TGS

5 Ordinate mode: %T

Abscissa mode: Wavenumbers (cm⁻¹)

Resolution: 4 cm⁻¹

Number of scans: 20

Phase KBr

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The X-ray powder diffraction patterns of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide are seen in Figure 2 and the crystallographic data in Table 2.

Table 2.

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| Crystallographic data of polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide | | | |
|--|--------|---------|-----------|
| No | 2θ | d | Rel I (%) |
| 1 | 3.680 | 23.9905 | 0.8 |
| 2 | 9.040 | 9.7745 | 49.7 |
| 3 | 11.840 | 7.4685 | 9.9 |
| 4 | 13.541 | 6.5339 | 11.1 |
| 5 | 14.060 | 6.2939 | 11.6 |
| 6 | 15.820 | 5.5974 | 7.6 |
| 7 | 16.320 | 5.4270 | 3.9 |
| 8 | 18.220 | 4.8651 | 4.6 |
| 9 | 18.459 | 4.8027 | 8.7 |
| 10 | 18.720 | 4.7363 | 13.6 |
| 11 | 18.940 | 4.6818 | 5.5 |
| 12 | 20.041 | 4.4270 | 5.0 |
| 13 | 20.380 | 4.3541 | 11.1 |
| 14 | 21.140 | 4.1993 | 3.5 |
| 15 | 21.939 | 4.0481 | 58.3 |
| 16 | 22.901 | 3.8802 | 13.8 |
| 17 | 23.340 | 3.8082 | 100.0 |
| 18 | 23.960 | 3.7110 | 3.3 |
| 19 | 24.480 | 3.6334 | 2.9 |
| 20 | 26.343 | 3.3805 | 3.6 |

Experimental

Instrument: Siemens D500

Wavelength: 0.1541 nm (CuKα₁)

55 Range: 3° - 33° (2θ)

Power: 40 mA/40 kV

Time: 1°/min (0.02°/step)

The following example illustrates the invention.

Example 1;

The crude synthesis product (3.0 kg) prepared according to the method described in British Patent Application 8727854 was dissolved in 8.0 kg of acetic acid (98-100%) (or formic acid) containing 80 g of hydrogen bromide (or 40 g of hydrogen chloride) by heating to 90 °C. The solution was slowly cooled to 20 °C and stirred for 20 h at 20 °C and finally for 6 h at 15 °C. The crystalline product was filtered and washed carefully first with a cold (4 °C) mixture (1 l) of toluene-acetic acid (1:1 v/v) and then with cold toluene (1 l). The product was dried in vacuum at 45 °C. Yield of crystallographically pure A form of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide was 2.4 kg (80%), m.p. 162-163 °C.

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Claims

15 1. The crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide characterized by the infrared spectrum in potassium bromide having the following absorption bands:

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| | Wavenumbers (cm ⁻¹) | Wavenumbers (cm ⁻¹) |
|----|------------------------------------|------------------------------------|
| | 3339 | 1512 |
| | 3092 | 1441 |
| | 3066 | 1377 |
| | 3039 | 1298 |
| 25 | 2981 | 1281 |
| | 2938 | 1210 |
| | 2217 | 1165 |
| | 1628 | 1150 |
| | 1607 | 800 |
| 30 | 1580 | 779 |
| | 1544 | 740 |

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35 2. A process for preparing the crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide of claim 1 which comprises crystallization of crude N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide from a lower aliphatic carboxylic acid containing a catalytic amount of hydrochloric or hydrobromic acid.

3. The process as claimed in claim 2, wherein said lower aliphatic carboxylic acid is acetic acid.

4. The process as claimed in claim 2, wherein said lower aliphatic carboxylic acid is formic acid.

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Claims for the following Contracting States: ES,GR

45 1. A process for preparing the crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-acrylamide characterized by the infrared spectrum in potassium bromide having the following absorption bands:

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| | WAVENUMBERS (cm ⁻¹) | WAVENUMBERS (cm ⁻¹) |
|----|------------------------------------|------------------------------------|
| 5 | 3339 | 1512 |
| | 3092 | 1441 |
| | 3066 | 1377 |
| | 3039 | 1298 |
| | 2981 | 1281 |
| | 2938 | 1210 |
| 10 | 2217 | 1165 |
| | 1628 | 1150 |
| | 1607 | 800 |
| | 1580 | 779 |
| | 1544 | 740 |
| 15 | | |

which comprises crystallization of crude N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide from a lower aliphatic carboxylic acid containing a catalytic amount of hydrochloric or hydrobromic acid.

20 2. The process as claimed in claim 1, wherein said lower aliphatic carboxylic acid is acetic acid.
 3. The process as claimed in claim 1, wherein said lower aliphatic carboxylic acid is formic acid.

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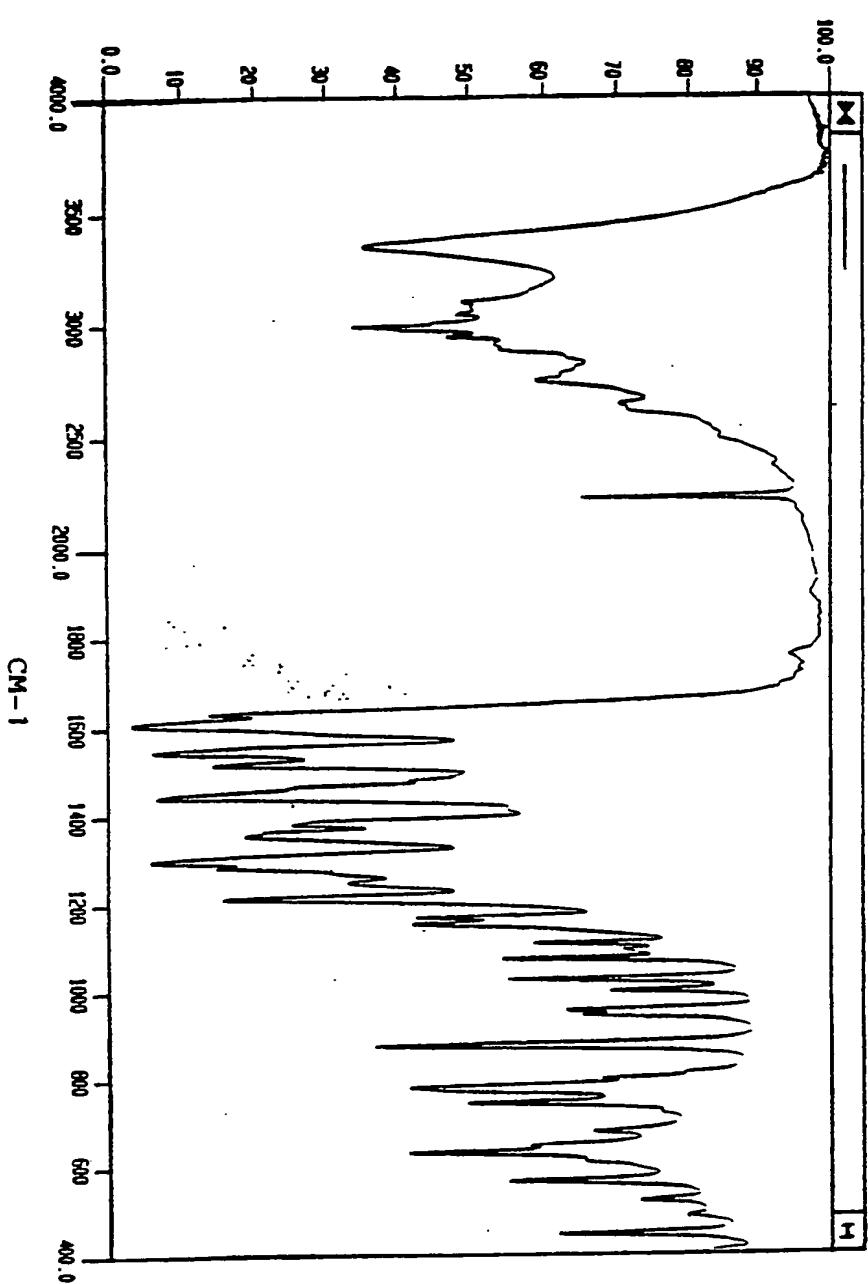


FIGURE 1. IR-spectrum of the polymorphic form A of
(E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

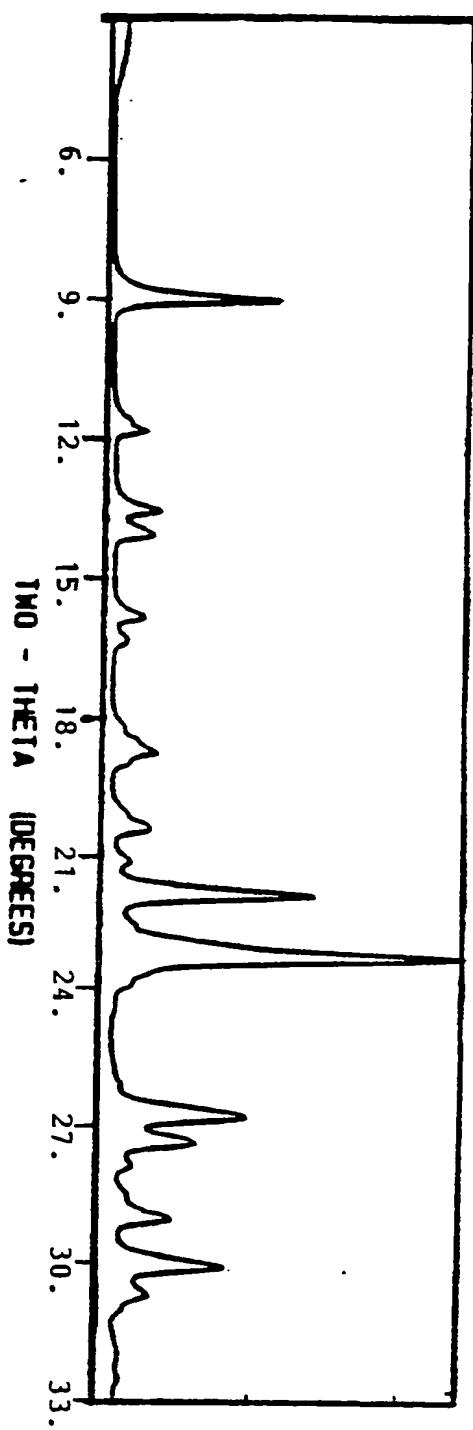


FIGURE 2. Standard X-ray powder diffraction pattern of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.



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08.05.91 Bulletin 91/19

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AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(86) Date of deferred publication of the search report:
06.05.92 Bulletin 92/19

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EP 0 426 468 A3



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EUROPEAN SEARCH REPORT

Application Number

EP 90 31 1963

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|--|---|--|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. CL5) |
| A | FR-A-2 607 493 (ORION-YHTYMA OY.) * page 57, example 100; claims 21-23 * | 1-4 | C07C255/41 |
| | | | TECHNICAL FIELDS SEARCHED (Int. CL5) |
| | | | C07C |
| The present search report has been drawn up for all claims | | | |
| Place of search | Date of completion of the search | Examiner | |
| THE HAGUE | 06 MARCH 1992 | ZERVAS B. | |
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